CENTER FOR DRUG EVALUATION AND RESEARCH

75-105

APPLICATION NUMBER:

BIOEQUIVALENCE

JUL 18 1997

Indapamide
1.5 & 2.5 mg tablet
NDA #75-105
Reviewer: J. Lee
75105SDW.397

Alphapharm Pty. Ltd
Brisbane, Australia
Submission date:
March 20, 1997

Review of an in-vivo Bioavailability Study, Dissolution Testing Data, and a Request for Waiver

Objective:

To assess the relative bioavailability of two indapamide tablet formulations (Alphapharm product vs Lozol®) after administration of single doses to fasted subjects.

Study Design:

The clinical study (#1785-1) was conducted by Biovail Corporation in Fargo, Toronto, Canada under the direction of Paul Y Tam, M.D., Medical Director and Principal Investigator..

Twenty-four healthy, non-smoking, male volunteers (plus two alternates) between the ages of 18-45 years and within ±10% of ideal body weight were successfully screened for the study.

All volunteers underwent a medical examination, physical examination and clinical laboratory tests which included hematology, clinical chemistry, hepatitis B-surface antigen, hepatitis C, HIV screens, urinalysis, and urine drug screens.

The selected volunteers exhibited normal findings in the physical examination, vital signs and ECG; clinical chemistry values were within ±10% of normal range unless deemed clinically insignificant by the Investigator.

Those subjects meeting any of the following criteria were excluded:

- known history or hypersensitivity to indapamide, sulfonamides, thiazide diuretics and/or related drugs.
- known history or presence of cardiac, pulmonary, GI, endocrine, neuromuscular, neurological, hematological, liver or kidney disease.
- known history of asthma, chronic bronchitis or other bronchospastic condition.
- use of regular medication or abuse of alcohol.

Selected subjects were not to have taken any medication (Rx and OTC) within 14 days of study

commencement nor during the study period. Subjects were instructed to abstain from consuming xanthine-containing products and alcohol 48 hours prior to each study period.

The study was designed as a open-label randomized, single-dose, two-way crossover study with a two week washout period between phases. The treatments consisted of a single (2x2.5 mg) dose of the following:

A. Indapamide
2.5 mg tablet (x2)
Alphapharm Pty Ltd., batch #PJ032A
Exiry date: 9/98

B. Lozol[R]
2.5 mg tablet (x2)
Rhone-Poulenc Rorer, batch #MN0723
Expiry date: 11/97

The dosing regimen for the selected subjects was as follows:

	Period I 11/10/96	Period II 11/24/96
sequence I	A	B
sequence II	B	A

sequence I - subj. #1, 2, 3, 4, 5, 7, 8, 12, 17, 19, 20, 21, 25

sequence II - subj. #6, 9, 10, 11, 13, 14, 15, 16, 18, 22, 23, 24, 26

*All subjects completed the crossover; however, the samples from only the first 24 subjects were analyzed per protocol.

After an overnight fast, subjects were given a 5 mg dose (2x2.5 mg) of the test or reference product with 240 ml of water. Fasting continued for 4.5 hours post-dose. Blood samples (10 ml) were collected in heparinized containers at 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72 and 96 hours. Volunteers were confined to the facility through the 24-hour blood draw, after which time they were allowed to leave the premises to return for subsequent blood draws. After collection, the whole blood samples were aliquoted into two polypropylene culture tubes and frozen at -25°C until assayed.

There were no adverse reactions nor protocol deviations reported during the study.

Analytical: [Not for release under FOI]

The samples were assayed for indapamide by a method

The linearity of the method as seen in the coefficients of variation (r) of the standard curves was >0.997 for all analytical runs. The coefficient of variation for the standard curves ranged from 2.35% (at 1280 ng/ml; n=28) to 5.91% (at 10 ng/ml; n=23). Standard curves were run in duplicate with each analytical batch.

The precision of the assay was monitored by four sets of QC samples that were run in duplicate with each group of samples. The data showed:

QC Value	Mean	%CV
15.00 ng/ml (n=28)	16.69	15.5
30.00 ng/ml (n=28)	29.89	9.10
240.0 ng/ml (n=27)	220.3	6.02
960.0 ng/ml (n=28)	927.7	5.08

Recovery data was obtained by comparing the mean peak height of extracted samples with the mean peak height of neat samples at four different QC concentrations. The results show that the overall percent recovery was 36.1% ±4.1% CV (n=8). The recovery for the internal standard was 51.0% ±1.3% CV (n=8).

The freeze-thaw (3 cycles) stability data in the study report were reported at 4 QC concentrations (15, 30, 240 and 960 ng/ml). There did not seem to be degradation through the first freeze-thaw cycle. However, after the second and third cycles, greater degradation occurred (see attached).

In-process stability was determined for the same 4 QC concentrations after 4 hours at room temperature. There was no appreciable degradation at any of the concentrations.

Long-term freezer stability at -25°C was reported to have been previously determined at up to 3 weeks at concentrations of 36.5 and 401.8 ng/ml in March 1992 (validation 102-00). Additional long-term stability tests are stated to be in progress (p. 959). No data was provided.

Data Analysis:

Indapamide concentration data in whole blood was analyzed by the SAS-GLM program to detect statistically significant differences ($p<0.05$) between formulations for the pharmacokinetic indices. Twenty-four datasets were used in the statistical analysis.

Results:

There were no statistically significant differences between the formulations for any of the PK indices. No sequence effects were noted for any PK parameter.

The 90% confidence intervals are presented below:

		90% CI n=24
ln-transformed scale	AUC_{0-t}	[98.3; 101.8]
	AUC_{inf}	[98.0; 101.4]
	C_{max}	[92.6; 100.8]

In-vitro Dissolution:

Dissolution testing was conducted on the bio-lots of the test and reference products using the USP method. The comparative profiles show Lozol to be a little slower in its drug release pattern than the Alphapharm product. Both products easily meet the Q. The resultant summary is attached.

Dissolution testing was also conducted on Alphapharm's 1.25 mg indapamide tablet vs Lozol 1.25 mg tablet in support of a waiver request for this strength.

Content Uniformity:

The assay for content uniformity for 10 dosage units of the Alphapharm product was 102.8% (CV=2.1%) of label claim; range = 98.4-106.0%; for Lozol, the assay was 100.0% (CV=1.5%); range = 97.6 - 101.6%.

Batch Size:

The batch size of the test product was not stated.

Waiver Request:

The sponsor has requested a waiver of in-vivo requirements for their 1.25 mg indapamide tablet. A quantitative formulation comparison between the 1.25 mg and 2.5 mg tablet was submitted, and comparative dissolution testing results were provided between the company's 1.25 mg test product vs Lozol® 1.25 mg tablet.

Comment:

1. The company did not submit the sample, standard and QC preparation and processing procedure. The company should submit the complete analytical methodology to include all aspects of sample handling, not just the description.

2. The freeze-thaw stability data for indapamide (p. 967) shows a large decline in concentration for the 30 and 240 ng/ml QC samples relative to the 15 and 960 ng/ml QC samples at the third freeze/thaw cycle. The sponsor should provide an explanation for this, including the impact this may have on the clinical sample values.

   The sponsor should re-validate the freeze/thaw stability procedure.

3. Long term stability data (for up to 3 weeks) was mentioned on page 959 of the study report, but was not submitted. This data was reportedly validated in March 1992 (validation 102-00) and additional long term stability tests were stated to be in progress. The duration of this study was much longer than 3 weeks. The sponsor should submit long term stability data that covers the duration of this study.

4. No raw data was provided in the study report except for those contained in the submitted chromatograms. The laboratory should submit all raw data (peak height data for drug and IS) for the analytical runs including those for the clinical samples, quality control samples, calibration standards and reassayed samples. The raw data should be organized with respect to the samples in each run..

5. The sponsor should state the assay methodology associated with the dissolution testing. The sponsor should also calculate and provide the percent CV information at each sampling time.

6. The sponsor should supply the batch size of the test product.

Recommendation:

The bioequivalence study conducted by Biovail Corporation for Alphapharm Pty Ltd. on its indapamide 2.5 mg tablet, comparing it to Lozol[R] 2.5 mg tablet, has been found incomplete by the Division of Bioequivalence per comments #1-6.

The company should address comments #1-6.

R. Lee 7/18/97

J. Lee
Division of Bioequivalence
Review Branch II

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FT INITIALED SNERURKAR 7/18/97

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(Fleischer), Drug File, Division File

USP XXIII Apparatus I Basket x Paddle _____ rpm 100

Medium: simulated gastric fluid w/o enzyme Volume: 900 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Lozol® tablet (Rhone-Poulenc Rorer)

Assay Methodology: not stated

Results

2.5 mg

Time (min)	Test Product Lot # PJ032 Mean % Dissolved	Range	(CV)	Reference Product Lot # MN0723 Mean % Dissolved	Range	(CV)
10	66		( )	53		( )
20	83		( )	71		( )
30	89		( )	79		( )
45	93		( )	86		( )
			( )			( )
			( )			( )

1.25 mg

	Lot # PH145			Lot # MN1361		
10	66		( )	61		( )
20	82		( )	72		( )
30	88		( )	78		( )
45	92		( )	82		( )
			( )			( )
			( )			( )

SUMMARY OF RESULTS

Mean Pharmacokinetic Parameters for Whole Blood Indapamide
(n = 24)

Parameter	Alphapharm 2 x 2.5 mg (Arithmetic Mean ± SD)	Lozol® 2 x 2.5 mg (Arithmetic Mean ± SD)
AUC (0 - t hours)(ng·hr/mL)	4753.47 ± 850.86	4747.72 ± 841.12
AUC (0 - infinity)(ng·hr/mL)	5078.95 ± 894.36	5092.82 ± 912.12
C_{max} (ng/mL)	239.15 ± 30.11	247.74 ± 32.13
T_{max} (hours)	1.63 ± 0.66	1.85 ± 0.94
$t_{1/2}$ (hours)	17.11 ± 2.21	17.08 ± 2.17
K_{el} (hour^{-1})	0.041 ± 0.006	0.041 ± 0.005

Alphapharm vs Lozol®

	AUC (0 - t hours)	AUC (0 - infinity)	C_{max}
90% Geometric C.I.[1]	98.26% - 101.83%	97.99% - 101.44%	92.56% - 100.81%
Ratio of Means[2]	100.03%	99.70%	96.60%
Intra-Subject C.V.[3]	3.60%	3.49%	8.61%

[1] 90% Geometric Confidence Interval using log-transformed data and Lozol® as the reference
[2] Calculated using geometric means according to the formula: $e^{(\text{Alphapharm} - \text{Lozol®})} \times 100\%$
[3] Intra-Subject coefficients of variation for log-transformed pharmacokinetic parameters

Mean WHOLE BLOOD INDAPAMIDE Concentrations (ng/mL)
(n = 24)

SAMPLE TIME (HOURS)	ALPHAPHARM 2 x 2.5 mg	LOZOL 2 x 2.5 mg
0.00	0.00 ± 0.00	0.00 ± 0.00
0.25	24.94 ± 51.59	29.52 ± 38.48
0.50	106.37 ± 74.82	110.63 ± 75.70
0.75	172.24 ± 70.35	161.95 ± 84.33
1.00	200.01 ± 65.88	181.07 ± 81.45
1.50	219.16 ± 44.24	202.61 ± 64.64
2.00	219.00 ± 23.33	217.79 ± 36.89
2.50	212.07 ± 23.62	212.96 ± 30.59
3.00	202.99 ± 21.95	207.51 ± 23.58
4.00	192.88 ± 23.86	197.08 ± 26.91
6.00	166.74 ± 19.03	168.38 ± 20.75
8.00	148.22 ± 16.38	151.99 ± 21.55
10.00	137.79 ± 21.72	138.11 ± 18.46
12.00	122.49 ± 16.65	122.59 ± 18.07
16.00	103.89 ± 16.81	105.35 ± 17.23
24.00	76.33 ± 14.32	76.86 ± 14.79
36.00	47.87 ± 13.07	48.09 ± 11.97
48.00	28.44 ± 8.90	28.16 ± 8.11
60.00	17.88 ± 7.79	17.83 ± 8.09
72.00	9.25 ± 7.22	8.76 ± 7.30
96.00	0.44 ± 2.16	0.00 ± 0.00

Section 6. **Bioavailability/Bioequivalence**

6.3 Formulae Comparison

6.3.1 Formulae Comparison Between Indapamide Tablets USP 1.25 mg (Alphapharm) and Indapamide Tablets 2.5 mg (Alphapharm)

A comparison of the Quantitative Formulation of Indapamide Tablets 1.25 mg USP (Alphapharm Pty. Ltd.) and Indapamide Tablets 2.5 mg USP (Alphapharm Pty. Ltd.) follows.

i- Tablet Contents

Ingredients	**Indapamide Tablets USP 1.25 mg**	**Indapamide Tablets USP 2.5 mg**
Indapamide	1.25 mg	2.50 mg
Lactose Monohydrate		
Microcrystalline Cellulose		
Maize Starch		
Povidone		
Magnesium Stearate		

*These are approximate weights only

Note:- Purified Water does not appear in the Finished Drug Product

The Manufacturer's Quantitative Formulation for the used in the Tablet Coating may be found on the following pages.

INDAPAMIDE VALIDATION

Table 7: Freeze/Thaw Stability of Indapamide

Results reported in ng/mL

Day of Analysis	Cycle		QC LOW1 15.00	QC LOW2 30.00	QC MED 240.00	QC HIGH 960.00
5	0		14.84	29.05	235.43	950.110
			16.50	28.77	226.93	945.47
		mean	15.67	28.91	231.18	947.79
	1		15.78	28.69	225.79	934.40
			15.37	28.14	227.71	920.80
		mean	15.58	28.42	226.75	927.60
		% difference	-0.6	-1.7	-1.9	-2.1
	2		14.36	24.53	202.64	837.21
			14.60	25.29	192.24	882.86
		mean	14.48	24.91	197.44	860.04
		% difference	-7.6	-13.8	-14.6	-9.3
	3		13.42	14.59	167.21	865.13
			13.74	24.07	166.36	873.08
		mean	13.58	19.33	166.79	869.11
		% difference	-13.3	-33.1	-27.9	-8.3

Note: Cycle 0 refers to samples analyzed with standards which have gone 1 F/T cycle prepared on Day 1.

USP XXIII Apparatus I Basket x Paddle _____ rpm 100

Medium: simulated gastric fluid w/o enzyme Volume: 900 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Lozol® tablet (Rhone-Poulenc Rorer)

Assay Methodology

Results

2.5 mg

Time (min)	Test Product Lot # PJ032 Mean % Dissolved	Range	(CV)	Reference Product Lot # MN0723 Mean % Dissolved	Range	(CV)
10	66		(3.7)	53		(4.7)
20	83		(1.5)	71		(2.7)
30	89		(1.6)	79		(2.2)
45	93		(1.1)	86		(1.8)
			( )			( )
			( )			( )

1.25 mg

	Lot # PH145			Lot # MN1361		
10	66		(3.2)	61		(7.1)
20	82		(1.8)	72		(6.7)
30	88		(1.9)	78		(6.9)
45	92		(1.7)	82		(5.9)
			( )			( )
			( )			( )